THERAPEUTIC EFFICACY OF PHOTOCHEMOTHERAPY IN VARIOUS DERMATOSES

Dissertation Submitted to

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY

in partial fulfillment of the regulations

for the award of the degree of

M.D. (Dermatology, Venereology and Leprology)

BRANCH – XII A

MADRAS MEDICAL COLLEGE

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY

CHENNAI, INDIA.

MARCH 2007

CERTIFICATE

Certified that this dissertation entitled "**THERAPEUTIC EFFICACY OF PHOTOCHEMOTHERAPY IN VARIOUS DERMATOSES**" is a bonafide work done by **Dr. SUBASHINI KARTHIKEYAN**, Post graduate student of the Department of Dermatology and Leprology and Institute of Venereology, Madras Medical College, Chennai- 3, during the academic year **2004 – 2007**. This work has not previously formed the basis for the award of any degree or diploma.

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DECLARATION

I, **Dr. SUBASHINI KARTHIKEYAN,** solemnly declare that the dissertation titled, "**THERAPEUTIC EFFICACY OF PHOTO-CHEMOTHERAPY IN VARIOUS DERMATOSES"** is a bonafide work done by me at Madras Medical College during 2004-2007 under the guidance and supervision of **Prof. Dr. B. PARVEEN, M.D.,D.D.,** Professor and Head, Department of Dermatology, Madras Medical College, Chennai-600 003. The dissertation is submitted to The Tamilnadu, Dr. M.G.R. Medical University, towards partial fulfillment of requirement for the award of **M.D. Degree in Dermatology, Venereology and Leprology (BRANCH – XII A).**

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SPECIAL ACKNOWLEDGEMENT

My sincere thanks to

Prof. Dr .KALAVATHI PONNIRAIVAN, B.Sc., M.D.,

DEAN,

Madras Medical College

for allowing me to do this
Dissertation and utilize the Institutional facilities.

ACKNOWLEDGEMENT

I am gratefully indebted to **Prof. Dr. B. Parveen M.D., D.D.,** Professor and Head, Department of Dermatology and Leprology for her invaluable guidance, motivation and help throughout the study. I would like to express my sincere and heartfelt gratitude to **Prof. Dr. V.S. Dorairaj, M.D., D.V.,** Director in charge, Institute of Venereology.

I wish to thank Dr. N. Gomathy M.D., D.D., Former Professor, Department of Dermatology and Dr. N. Usman M.D., D.V., Ph.D., Former Director, Institute of Venereology for their constant support and motivation.

I am very grateful to Dr. S. Jayakumar M.D., D.D., Additional Professor, Department of Dermatology for his invaluable guidance and help. I sincerely thank Dr. C. Janaki M.D., D.D., Reader of Dermatology (Mycology) for her priceless support.

I express my earnest gratitude to Dr. D. Prabavathy M.D., D.D., Professor and Head of Department of Occupational Dermatology and Contact Dermatitis for her constant motivation and guidance. I thank Dr. V. Somasundaram M.D., D.D., Additional Professor, Department of Occupational Dermatology and Contact Dermatitis for his benevolent help and support.

I express my sincere gratitude to Dr. K. Rathinavelu M.D., D.D., Professor of Leprosy and Dr. R. Arunadevi M.D., D.D., Lecturer/Registrar, Department of Dermatology for their support.

I am inclined to thank Dr. R. Priyavathani M.D., D.D., D.N.B., Dr. V. Anandan M.D.,(Derm), D.C.H., D.N.B.,(Paed) and Dr. G.K.Tharini M.D., Dr. M. Vijayanand M.D., Assistant Professors, Department of Dermatology for their kind support and encouragement.

I thank Dr. A. Hameedullah M.D., D.D., Dr. S. Kumaravelu M.D., D.D., Dr. J. Manjula M.D., D.N.B., (Derm) and Dr. Aftab Jameela Wahab M.D., D.D., Assistant Professors, Department of Occupational Dermatology and Contact Dermatitis for their support and help.

My sincere thanks to Dr. S. Mohan M.D, D.V. Former Registrar, Dr. V. Thirunavukkarasu M.D., D.V., Dr. K. Venkateswaran M.D., D.V., Dr. P. Elangovan M.D., D.V., Dr. D. Ramachandra Reddy M.D., D.V., Dr. S. Thilagavathy M.D., D.V., Dr. P. Mohan M.D., D.V., Dr. S. Arunkumar M.D., D.V., and Dr. S. Kalaivani M.D., D.V., Assistant Professors, Institute of Venereology for their help and suggestions.

I am also thankful to Dr. K. Manoharan M.D., D.D., and Dr. V. Sampath M.D., D.D., for their continuing guidance and support.

I duly acknowledge the Paramedical staff and my colleagues for their help and favour.

Last but not least I am profoundly grateful to all patients for their cooperation and participation in the study.

CONTENTS

INTRODUCTION

Photochemotherapy is one of the oldest known light dependant therapies in medicine.

Psoralen photochemotherapy is a combination of psoralen and long wave ultraviolet radiation that brings therapeutically beneficial results not produced by either drug or irradiation alone. Initially plant sources of psoralen were used and patients were exposed to sunlight for a specified period. This method has been modified over several years and synthetic drug preparations and also artificial sources of light have been introduced. This has made possible the accurate measurement of the UV dose given and also helped in better treatment results.

Initially photochemotherapy was used in the treatment of vitiligo. Gradually its uses have expanded and is currently being used in the treatment of several common and uncommon skin diseases.

But PUVA has also got various side effects which are both acute and long-term effects. Higher cumulative dosage is known to cause various skin cancers. Hence appropriate administration and regular monitoring is very essential. Also PUVA therapy requires good patient compliance and regular treatment schedules.

Thus if the correct category of patients are selected and PUVA administered as per various guidelines mentioned it can indeed be an extremely beneficial therapy for various diseases.

The study here includes the efficacy of PUVA in various common skin conditions encountered in the Dermatology department.

REVIEW OF LITERATURE

HISTORY

The concept of photochemotherapy or the therapeutic use of chemical in conjunction with radiation existed more than 3000 years ago. Its first use was documented in ancient Hindu scriptures[1]. Psoralens are derived from plants such as Ammimajus found in Egypt and Indian plant such as Babachee which is also called Psoralia corylifolia. Psoralens have been found in more than 30 plants such as lime, lemon, bergomet, parsley, celery, fig and cloves. ElMofty at the University of Cairo first used a purified psoralen obtained from the plant Ammi majus for the treatment of vitiligo. Methoxalen(8-methoxypsoralen,8-MOP) was introduced to the United States in 1951. Trioxalen 4, 5, 8 Trimethyl psoralen a synthetic compound was introduced in 1964.

Finally psoralen chemotherapy as it is commonly applied today was introduced in 1974 when investigations at the Massachusetts general hospital reported complete clearing in 21 patients treated with systemic 8-MOP followed by newly developed high intensity radiation provided by Sylvania[2] .The acronym PUVA was introduced by the same group. Bath PUVA originated in Scandinavia.

PSORALENS AND PHARMACOKINETICS

Psoralen and many of its derivatives are naturally occurring tricylic furocoumarins. The derivatives most widely used are:

1. 8-Methoxypsoralen (8-MOP, methoxsalen, xanthotoxin)

It is one of the most commonly used drugs in our country. It is lipophilic and poorly soluble in water.

Pharmacokinetics:

It is absorbed from gastrointestinal tract when taken orally. The factors affecting absorption include:

1. Physical formulation of the compound- Liquid preparations are better absorbed, peak levels occurring one hour earlier when compared to crystalline preparations[3]. More important the total dose of UVA radiant energy was reduced by 40%.These liquid preparations have been approved by the FDA and are available in USA from March 1987.

2. Diet- It did not very much affect the bioavailability of 8-MOP but a high fat diet retarded the absorption of 8-MOP[3]. Thus psoralen is best given under fasting condition even though nausea may be a problem.

3. Inter and intra individual variation- This may occur due to varied intestinal absorption, first pass metabolism and elimination of the drug.

Metabolism:

Psoralens are metabolized in the liver by CYT P450 dependant microsomal enzymes. 8-MOP has a serum half life of 1hour and are degraded within 12hours and excreted mainly in the urine. Within the same individual, serum levels of 8-MOP correspond with skin reactivity, the peak of skin photo toxicity coinciding with peak serum levels[4]. Individuals with a high clearance and low maximum serum concentration usually show reduced sensitivity to PUVA[5]. These patients are those not responding to the usual dose, they may respond to higher dose of psoralen or to the administration of the drug by other routes such as bath water delivery. Psoralen appears to be distributed to all cell tissues after oral administration and there is no risk of accumulation in any organ in patients with normal liver and kidney function.

Dosage-0.6 to 0.8mg/kg body weight

2. 5-Methoxy psoralen (Bergapten).

This differs structurally from 8-MOP in the position of the methoxy group on the coumarin ring. It is less water soluble and has an intestinal rate of absorption of only 25% that of 8-MOP.It is rapidly metabolized with a serum half life of 1 hour. The advantages are lower incidence of short term side effects such as nausea, vomiting, pruritus and phototoxicicity[6]. On the other hand it causes higher degrees of pigmentation and requires greater cumulative UVA dosage. A new

micronised tablet has been developed which has increased bioavailability, increased efficacy and decreased adverse effects.

Dosage:-1.2-1.5mg/kg body weight

3. 4,5,8 Trimethylpsoralen(TMP, Trioxsalen)

It is a synthetic compound which is less phototoxic after oral administration. It has minimal gastrointestinal absorption. A peak serum concentration is reached 2 hours after ingestion. The plasma level after oral therapy is usually not sufficient enough for Psoriasis treatment but effective for vitiligo therapy[7].

TMP is efficiently and predominantly used via Bath water delivery[8]

Dosage- 0.3 to 0.8 mg/kg body wt.

In USA, Food and Drug administration approved the use of psoralen in PUVA therapy in May 1982.[3]

4.Newer compounds:-

They include Angelicins (angular furocoumarins) and substituted psoralens (Pyridopsoralen).These compounds are reported to produce less erythema and have good antipsoriatic activity.[9,10.] Hence it is useful in the treatment of psoriasis.

Psoralen photochemotherapy and mechanism of action:

Ground state psoralen molecules are activated to the excited singlet state by absorption of photons in the UVA wave band. The peak of absorption spectrum is around 320-330nm.

Mode of action of psoralens occurs at the following levels:[11]

1. Cell nuclei (DNA and chromatin)-Type 1 reaction
2. Cell membrane of epidermal, dermal and endothelial cells - Type 2 reaction
3. Cytoplasmic constituents (enzymes, RNA, lysosomes, etc) - Type 2 reaction.

Type 1 reaction-

It is an anoxic reaction not requiring oxygen and the site of cellular damage is primarily in the DNA of cell nuclei. In the first step of this photochemical reaction a monofunctional adduct with thymine or cytosine is formed. Some psoralens, including 8-MOP, TMP and 5-MOP can absorb a second photon and this reaction can lead to the formation of a bifunctional adduct with 5, 6 double bond of the pyrimidine base of opposite strand, thus producing an interstrand cross-link of double helix. This intercalation of psoralen with epidermal DNA produces a suppression of both DNA synthesis and cell division. It can revert pathologically altered pattern of keratinocytes differentiation markers and reduce the number of proliferating epidermal cells.

This type 1 reaction occurs immediately and subsequently cell proliferation is also inhibited in patients with psoriasis who receive PUVA treatment.

Type 2 reaction-

In this reactive oxygen species induce oxidation of cellular lipoprotein membrane lipids, destruction of membrane bound cytochromes P-450, and the activation of the cyclooxygenase pathway, which results in an increase of secondary oxidation products that contribute to increased synthesis of eicosanoids. The reactive oxygen species can directly damage DNA by generating DNA strand breaks.

PUVA down regulates certain lymphocytes and antigen presenting cell functions, influences adhesion molecule expression, diminishes Langerhan cell numbers within epidermis. PUVA also affect specific cells such as lymphocytes and polymorphonuclear leucocytes. A decrease in the percentage of T lymphocytes following PUVA treatment has been reported. [12] Infiltrating lymphocytes are strongly suppressed by PUVA and PUVA can induce apoptosis in lymphocytes.

Psoralens also stimulate melanogenesis. This involves the photoconjugation of psoralens in melanocytes, mitosis and subsequent proliferation of melanocytes, an increased formation and melanisation of melanosomes, increased transfer of melanosomes to keratinocytes and increased synthesis of tyrosine mediated by stimulation of C-AMP

activity. It may also correct the structural abnormalities in the melanocytes in vitiligo skin.

Ultraviolet Radiation spectrum and PUVA

Sunlight comprises of a spectrum of electromagnetic waves as follows

1. Gamma and Cosmic rays - Range <100nm
2. Ultraviolet rays - Range 100-400nm
3. Visible spectrum - Range 400-700nm
4. Infrared rays - Range >700nm.

The ultraviolet range includes

UVA: 320-400 nm

UVB: 280-320nm

UVC: 100-280nm.

The PUVA action spectrum is defined as the effectiveness of clearing psoralen- sensitized psoriasis as a function of wavelength. Currently broad band high intensity UVA sources ranging from320-400nm with a peak emission at 352nm are typically used in PUVA. [13]

The LIGHT SOURCES:

The commonly used lamps are

1. Flourescent lamps
2. Metal halide lamps

Fluorescent lamps are low pressure mercury arc discharge sources encased in phosphor coated glass. The mercury arc discharge source releases radiation that is absorbed by phosphor, which undergoes excitation, re-emitting energy at longer wavelength via fluorescence. [14]

Metal halide lamps are medium to high pressure mercury arcs housed within quartz. The type of filter used with each lamp determines its emission spectrum.

PHOTOSENSITIVITY EFFECTS OF PUVA:

1. It produces an inflammatory response that manifests as delayed phototoxic erythema. [14,15.] It does not appear before 24 hours to 36 hours and it peaks at 72-96 hours.
2. Pigmentation is the second important effect .It maximizes 7 days after a PUVA exposure and may last from several weeks to months.
3. Intense pruritus and sometimes peculiar stinging sensation in the affected area may occur as a consequence of damage to superficial nerve endings.

TREATMENT PROCEDURES

Preliminary tests to be done before starting PUVA are

1. Complete Hemogram
2. Blood urea, serum creatinine, blood sugar
3. Liver function tests
4. Ophthalmological evaluation to rule out cataract

The contraindications to PUVA[16] which are to be excluded before starting treatment are

1.Absolute contraindications:

a. Xeroderma pigmentosum, Blooms syndrome and congenital photosensitivity disorders
b. Lupus erythematosus
c. Pemphigus and Pemphigoid[17]
d. History of idiosyncratic reactions

2. Relative contraindications:

a. Concurrent photosensitivity medications
b. Prior exposure to ionizing radiation or arsenic[18]
c. History of skin cancer/chronic actinic damage[18]
d. Personal or family history of melanoma[19]
e. Pregnancy, lactation[20]
f. Age <18 years

g. Significant renal, hepatic or cardiac dysfunction[13]

h. Cataract[21]

The initial UVA doses are established either by skin types or by minimal phototoxicity dose testing (MPD). [22]

Skin Phototypes		Recommended Dose
1	Always burn never tan	0.5 j/cm^2
2	Always burn sometimes tan	1.0 j/cm^2
3	Sometimes burn, always tan	1.5 j/cm^2
4	Never burn sometimes tan	2.0 j/cm^2
5	Moderately pigmented	2.5 j/cm^2
6	Deeply pigmented	3.0 j/cm^2

Types 1 to 4 are determined by history

Types 4 to 6 by physical examination

Determination of MINIMAL PHOTOTOXICTY DOSE (MPD): [23,24.]

One hour after administration of oral psoralen, a template is placed on the patient's buttocks, as it is the area of greatest UV sensitivity. The template consists of 6 to 8 areas of at least 1 cm^2, which can be exposed

to increasing doses of UVA. Visual assessment of the erythema response is preformed at 72hours using a grading scale. The MPD is the lowest dose that produces pink erythema with distinct borders 72hours after exposure. A fraction of this dose e.g. 50-80% is frequently used as a starting dose in PUVA therapy.

Among these two methods, the best way to begin PUVA therapy is to determine patients MPD. [25] It ensures that the patients will receive a starting dose that is neither too high resulting in phototoxicity nor too low causing ineffective therapy. Another potential advantage if the MPD is that, fewer treatments are needed and thus the carcinogenic potential may be lower [26]

To increase or maximize the efficacy of PUVA treatment and to reduce the treatment duration and cumulative dose, a weekly minimal phototoxic dose was introduced. [27] There is a substantial advantage from this logical approach.

INDICATIONS FOR PUVA THERAPY [28,29.]

FDA approved

1. Psoriasis
    a. Chronic plaque type of psoriasis involving greater than 20% body surface area
    b. Erythrodermic psoriasis

c. Generalized pustular psoriasis

d. Palmoplantar psoriasis

2. Vitiligo[30]

Other uses include

3. Mycosis fungoides
4. Lymphomatoid papulosis
5. Pityriasis lichenoides
6. Langerhan cell histiocytosis
7. Atopic dermatitis[13]
8. Seborrhoeic dermatitis
9. Chronic hand eczema
10. Pityriasis rubra pilaris
11. Generalised lichen planus[31]
12. Lichen nitidus
13. Alopecia areata
14. Cutaneous graft versus host disease[32]
15. Morphoea
16. Urticaria pigmentosa
17. Aquagenic pruritus
18. Chronic urticaria
19. Actinic prurigo[33]
20. Nodular prurigo[29]

21. Pityriasis alba[34]
22. Generalised granuloma annulare
23. Grovers disease
24. Pigmented purpuric dermatosis
25. Scleredema adultorum[35]

PUVA for prevention of disease-

In certain conditions, small doses of PUVA are given for a specified period and this will lead to desensitization. They include:

1. Polymorphic light eruption[36]
2. Hydroa vacciniforme
3. Solar urticaria
4. Erythropoietic protoporphria
5. Chronic actinic dermatitis

ADVERSE EFFECTS

Short term:

A. Phototoxic reactions:

1. Erythema and frank sunburn- most common side effects(30%)[37]
2. Pruritus (25%)[38]
3. Sever cutaneous pain- It is a rare symptom and starts at 4-8 weeks after onset of PUVA therapy and sometimes after treatment has been stopped. Attacks may last from 15mins to several hours, and

can be provoked by scratching or pressure. The buttocks and limbs are particularly affected, especially at night. The pain is not associated with itching. It settles over a few weeks. [39,40]

4. Blistering on hands and feet.
5. Photoonycholysis and pigmentation of nails[41]
6. Phytophotodermatitis

B. Due to psoralen:

1. Nausea and vomiting (12%)
2. Headache
3. Dizziness
4. Bronchoconstriction
5. Hepatotoxicity[42]
6. Drug fever
7. Exanthems

Other side effects:

1. Hypertrichosis of the face especially in females[43]
2. Mild facial dermatitis resembling seborrhoeic dermatitis and involving the glabella, cheeks and nasolabial folds
3. Acneform eruptions
4. Pigmentation- diffuse or poikiloderma like or in a naevus spilus like pattern, producing gross freckling (PUVA Lentigenes). [44]
5. Induction of bullous pemphigoid.[45]

6. Lichenoid eruptions and histology of unaffected skin may show colloid or amyloid bodies in dermo epidermal junction. [46]
7. Rarely abnormal liver function tests may occur and psoralens are known to induce liver microsomal enzymes. [47]

PUVA erythema is the most commonest phototoxic reaction.[42] Cool bath, aspirin, antipruritics and topical steroids may be given. Pruritus may be relieved by capsaicin. For very severe pruritus, phenytoin 150mg BD may relieve the symptoms.

Gastrointestinal side effects like nausea and vomiting can be overcome by either

1. Ingesting 8-MOP with food
2. Reducing the dose or
3. Using 5-MOP instead of 8-MOP which is less nauseating.

The concurrent administration of other photoactive drugs increase the chances of unpleasant erythematous reactions.[48] Worsening or new eruptive psoriasis, resulting from a Koebner phenomenon, occurs in about 2% of patients.

Lupus erythematosus like syndrome can rarely occur and ANA titer and circulating immune complexes may be raised. [49]

Long Term adverse effects

1. Chronic actinic damage
2. Carcinogenesis
3. Immunological
4. Ophthalmological

1. Chronic actinic damage-[50]

Premature photo ageing may be a consequence of high cumulative UVA exposure associated with long term PUVA therapy. It results due to damage to collagen and elastin. PUVA lentigenes exhibit irregular borders and uneven pigmentation. The melanocytes are abnormal within these lentigenes, with large melanosomes and lipid accumulations.[51] These changes may be partially reversible. Actinic kertoses may occur. A case of superficial actinic porokeratosis has been reported.[52]

2. Carcinogenesis-

This is due to reactivity of psoralens with DNA forming mono and bifunctional adducts. PUVA induced downregulation of immune responses may play an additional role.

Long term use of PUVA has been clearly associated with increased risk of developing cutaneous squamous cell carcinoma and basal cell carcinoma. However more recent advances indicate an increased risk of squamous cell carcinoma.[53] Stern found a specific increase of cutaneous

carcinoma in the genital skin of male patients.[54] Shielding of genitalia during PUVA reduces the risk.

There is also an increased risk (8.4 fold) of malignant melanoma in patients who receive high dose PUVA. So it is best avoided in those predisposed to malignant melanoma (those with numerous melanocytic naevi or atypical moles and a family history of melanoma). [55]

Most studies thus advice to keep cumulative dose of PUVA low and use it in a rotational therapy or sequential therapy with other drugs.

3.Immunological effects-

Reduction in circulating T-lymphocytes numbers and function is documented. [56] A reduction in circulating helper –inducer T cells may also occur with long term PUVA therapy. Inhibition of lymphocyte DNA synthesis occurs. Delayed hypersensitivity responses are reduced and may be caused by Langerhan cell depletion or damage in the irradiated skin. [57]

4. Ophthalmological effects-

Evidence of psoralen induced cataract is mainly based on experimental studies. However bilateral punctate cortical opacities have been reported.

Because some uncertainty remains about the risk of eye toxicity, it is recommended that appropriate UVA opaque spectacles be worn during

the entire period of increased photosensitivity after psoralen ingestion. Obviously there is no risk with topical or bath PUVA.[58]

DRUG INTERACTIONS

Photosensitizing medications such as tetracyclines, phenothiazines, sulfa drugs and thiazide drugs may lead to additive phototoxicity and therefore preferably avoided.

Reduced levels of 8-MOP may occur with concomitant phenytoin treatment. This is due to the induction of hepatic enzymes. Similar modifications may also occur with barbiturates and alcohol.

OTHER FORMS OF PUVA THERAPY

TOPICAL PUVA

Application of psoralens in creams, ointments or lotions followed by UVA radiation is effective in clearing psoriasis. Two psoralens are currently used topically

1. TMP(4,5',8 Trimethyl psoralen, Trioxsalen)
2. 8-MOP(Methoxypsoralen, Methoxalen)

TMP is more potent topically. The photosensitivity action spectrum is within the range of 330-340nm.After application of 8-MOP or TMP as an ointment ,cream or alcoholic solution, there is gradual increase in photosensitivity in the first hour that remains high for several hours.

Technique:

8-MOP or TMP in a suitable vehicle is applied to the skin area to be treated. Irradiate it when photosensitivity is maximal, 1 hour after application. Immediate irradiation may be tried.[59] The skin is cleansed with soap and water immediately after irradiation to decrease photosensitivity. The main disadvantages are:

a. Application is laborious and time consuming.
b. Nonuniform distribution on the skin surface induces unpredictable phototoxic erythema and irregular patches of pigmentation. [60]
c. Allergic contact and photocontact dermatitis.[61] Use of topical PUVA is now limited to psoriasis of palms and soles.

BATH PUVA

It consists of 15 to 20 minutes of whole body immersion in a solution of 8-MOP. Irradiation needs to be performed immediately as photosensitivity decreases rapidly. Dose-0.5to 0.8mg is used per liter of water.

Advantages:

1. Uniform drug distribution over skin surface
2. Very low plasma psoralen levels and hence gastrointestinal and eye toxicity can be avoided.
3. Lower cumulative UVA dose and therefore less carcinogenic risk.

For bathing suit delivery the patient is enclosed in a polythene bag with 4litres liquid for 15mins, concentration of 0.5 and 3.75mg may be used. Advantages of bath suit delivery are:

1. It requires only less amount of water and psoralen solution.
2. It can be carried out at home with sunlight as the UVA source (PUVA SOL).
3. The cost of the drug is less compared to water delivery and UVA source.
4. Systemic side effects like nausea and cataracts do not occur.
5. Easy and less time consuming.

Disadvantages:

1. The entire body surface especially the head does not common in contact with the drug.
2. The concentration of the drug may not be uniform in bath suit.

HAND and FOOT PUVA units are also available-This can be used for treatment of localized disease.

Mouth PUVA:[62]

This new variant of PUVA therapy was tried for oral lichenoid lesions using topical application of Trioxsalen ointment.

PUVA – Turban:[63]

This is another method to treat Alopecia areata. In this method, a cotton towel is soaked in diluted bath water solution containing 8-MOP

(0.0001%, 1 mg/ml) at 37^{o} C. It is wrung gently to remove excess water and wrapped around patient's head in a turban fashion for 20 minutes. This is directly followed by UVA radiation.

Several modes of delivery of psoralens are under research. It was found that sublingual delivery of psoralen in skin type 1 and 2 may be useful.[64] It reduces the risk of hepatic and renal damage in patients who already have dysfunction of these two organs. Side effects like nausea and intolerance are also reduced.

PUVA FOR PSORIASIS:

PROTOCOLS:

Many protocols have been used and although they are slightly different, they share the same basic principles of using regularly repeated PUVA exposures. Generally PUVA protocols have 2 phases

1. Clearance phase-Aimed at psoriasis suppression
2. Maintenance phase characterized by a tapering to a minimal number of regular visits in an effort to maintain and extend remission.

There are 2 classic protocols- The **American** and European schedules. [65,66]

DIFFERENCE BETWEEN US AND EUROPEAN PROTOCOLS:

	UNITED STATES	EUROPE
UVA dosimetry	Predetermined dose according to skin phototype	Individualized dose according to MPD determination
Frequency of treatments	2-3 times/week	4 times/week
Dose increments	Predetermined	Individualized
Principle of approach	Rigid and cautious	Flexible and aggressive
Goal	To clear without ponderance testing and acute side effects	To clear rapidly before maximum pigmentation develops

Skin photo type dependant dosimetry in American protocol[67]

Skin type	***Initial dose*** *(J/cm^2)*	***Increments*** *(J/cm^2)*
1	1.0	0.5
2	2.0	0.5
3	3.0	0.5
4	4.0	1.0
5	5.0	1.0
6	6.0	1.0

The study results of a Us Cooperative Clinical Trial (USCCT) and European Protocol Study (EPS) for treatment of psoriasis[68,69]

	USA	EUROPE
No of patients	1139	3175
Results better than marked improvement	1005(85%)	2785(89%)
Exposures required for clearing *(median)*	25	20
Duration of treatment *(weeks)*	12.7	5.3
Cumulative dose *(J/cm^2)*	245	96

Indian skin comes under 4 and 5 phototype and is usual to start with 4.5 J/cm^2 and increments of 0.5 J/cm^2 based on skin response.

Maximum UVA dose that can be reached is

1 and 2	8-12 *J/cm^2*
3 and 4	12-16 *J/cm^2*
5 and 6	16-20 *J/cm^2*

Maintenance schedule:

The final clearance dose of radiation is held constant and frequency of treatments gradually reduced. If a significant (>5%) amount psoriasis begins to return, the frequency of treatment can be increased or the clearance schedule restarted.

Combination treatment:

Topical combination-PUVA has been combined with other treatment form to improve efficacy and to reduce possible side effects. Topical adjuvant therapies include glucocorticoids, anthralins, tar and recently calcipotriol and tazarotene.

Methotrexate:

The combination of PUVA and Methotrexate can reduce the duration of treatment, number of exposures and is also effective in clearing psoriasis unresponsive to PUVA or UVB alone. Methotrexate is begun three weeks before PUVA therapy in a dosage of 2.5 to 5 mg at 12h intervals for three days each week. This is continued throughout the clearance phase of PUVA therapy.[70] Methotrexate is also delivered at a total dose well below the minimum dose reported for hepatotoxicity. This combination if used for a long time could be hazardous because PUVA and Methotrexate may act synergistically in the development of skin cancers.

RETINOIDS: RE-PUVA

The therapeutic efficacy of PUVA is dramatically increased when combined with Retinoids. Etretinate and Acitretin are administered daily 2 weeks prior to initiation of PUVA and this combination is continued throughout the clearing phase. RE-PUVA reduces the number of exposures and the total cumulative UVA dose and also clears the disease

in those patients who could not be brought into remission with PUVA alone. As an additional benefit, retinoids may protect against long term carcinogenic effects of PUVA mainly by reducing the number of exposure and also by their cancer protective effect.

PUVA FOR VITILIGO

Psoralen photochemotherapy is one of the effective therapies in vitiligo. The exact mechanism of repigmentation of individual skin in vitiligo cannot be clearly defined.

The following hypothesis has been proposed in vitiligo. [71]

1. Reactivation of inactive melanocytes in the vitiliginous patches.
2. Release of an inhibited tyrosinase enzyme
3. Induction of migration of active melanocytes from surrounding normal epidermis and hair follicles.
4. Increased tolerance to UV exposures and thereby stronger stimulation of the melanocytes
5. Correction of the structural abnormalities in the melanocytes in vitiligo skin.

The chemical observation of perifollicular repigmentation in vitiligo is an early change after PUVA therapy. There is activation of melanocytes located in outer root sheath of hair follicle which divide,

proliferate and migrate upward to achromic areas, visible as follicular pigmentation clinically. [72]

PUVA may deplete VAMA (Vitiligo associated antigen) and impair the function of Langerhan cell, thus blocking the immune induced damage. Recently it was found out that leucotriene C_4 and TNF-α released by keratinocytes secondary to UV damage causes melanocyte migration in vitro. [73]

Oral 8-MOP and TMP are the photosensitisers used frequently. To induce repigmentation, patients need constant long term therapy (12-24 months). Because oral TMP is much less phototoxic than 8-MOP, it is preferred for treatment with sunlight as radiation source. Responsiveness is defined as the development of perifollicular macules of repigmentation.

Topical 8-MOP is used in the concentration of 0.05% to 0.1% in Vitiligo in patients with less than 20% body surface involvement.

The treatment is started at low dose of 4j/cm2 of UVA and subsequent increments made until a uniform erythema occurs over the lesions or a total dose of 8j/cm2 is reached and treatments are given twice a week.

The perifollicular repigmentation is usually seen after 5weeks of alternate day therapy (approximately 15 treatments).Face and neck areas respond much better than lips, finger tips and bony prominences.

Various international studies have shown the effect of PUVA in vitiligo. A ten year study was done in St. Johns Institute of Dermatology, UK showing the efficacy of PUVA in widespread vitiligo.[74]

PUVA for PARAPSORIASIS and CUTANEOUS T CELL LYMPHOMAS:

PUVA is also effective in the treatment of Parapsoriasis. A large clinical trial done in Germany shows the effect of PUVA in various types of parapsoriasis. [75]

PUVA is dramatically effective in early stages of Cutaneous T-Cell Lymphomas (1A and 1B) when it induces complete and long lasting remissions. [76] The mode of action is direct phototoxic destruction of the atypical cells in epidermis and dermis.

Treatment schedule and dosimetry in photochemotherapy include clearing phase, a maintenance phase and follow up phase without therapy. The initial treatments consists of two exposures per week for 1 month and one exposure per week for 2 months .The patient is monitored regularly after stopping treatment.

In later stages PUVA may reduce the tumor cell burden and thus act synergistically with other treatment. [77]

PUVA FOR LICHEN PLANUS:

PUVA is an effective alternative for systemic steroids in generalized Lichen planus. A bilateral comparative study done in the US shows the efficacy of PUVA in generalized Lichen planus.[78] However Lichen planus may become resistant to treatment with PUVA than psoriasis.

Bath PUVA can also clear Lichen planus and combined PUVA-Etretinate may accelerate clearing. [79]

AIM OF THIS STUDY

BACKGROUND:

Photochemotherapy is an efficient method of treating various dermatological disorders. With appropriate administration and regular monitoring it can be used safely in the treatment of various common dermatoses.

OBJECTIVES:

1. To evaluate the efficacy of PUVA therapy in the treatment of
    a. Psoriasis vulgaris involving >20% of Body surface area,
    b. Vitiligo vulgaris involving >20% of Body surface area,
    c. Generalized lichen planus and
    d. Parapsoriasis.
2. To asses the side effects of PUVA during treatment.
3. To observe the patient compliance for PUVA therapy.

MATERIALS AND METHODS

55 patients who attended the out patient clinic at the Department of Dermatology, Government General Hospital, Chennai were included in the study.

Selection criteria:

1. 20 patients with psoriasis vulgaris involving greater than 20% of the body surface area.
2. 20 patients with stable vitiligo vulgaris involving greater than 20% of the body surface area.
3. 10 patients with generalized lichen planus
4. 5 patients with large plaque parapsoriasis.

The diagnosis of Psoriasis, Vitiligo and Lichen planus was made on clinical grounds.

The diagnosis of Parapsoriasis made based on skin biopsy and Histopathological examination.

Exclusion criteria:

1. Age less than 18 years
2. Pregnant and lactating women
3. Photosensitive disorders
4. Significant hepatic, renal, cardiac dysfunction
5. Family history or previous history of malignant melanoma

6. H/O inorganic arsenic intake or ionizing radiation
7. H/O skin carcinoma or photo damage
8. Chronic alcoholics
9. Active infection like tuberculosis
10. Cataract
11. Systemic therapy within 8 weeks.

All patients were explained about the disease and the benefits and side effects of the drugs were discussed with them. Consent was obtained from all patients before initiation of therapy.

All patients were evaluated as follows:

1. History-The onset and duration of the disease, h/o any drug intake, h/o any photosensitive diseases, etc were taken
2. General examination
3. Systemic examination
4. Dermatological examination
5. Ophthalmological evaluation
6. Investigations:
    a. Complete hemogram
    b. Urine analysis
    c. Blood sugar, urea, creatinine
    d. Liver function tests

TREATMENT PROTOCOL AND METHODOLOGY

The study population included

Group 1: 20 patients with Psoriasis vulgaris.

Oral 8-methoxypsoralen crystalline tablets (10mg) at a dose of 0.6mg/kg rounded up to the nearest 10mg was advised to be taken in empty stomach. After 2 hours, they were exposed to UVA radiation in the UVA cabinet. The starting UVA dose was determined by skin type according to the U.S treatment protocol. Treatment was given twice weekly on Mondays and Thursdays. Patients were advised to wear UV blocking sunglasses during exposure in the cabinet and also for 24hours after treatment. Men wore genital protection in the cabinet. UV irradiance of the cabinet was measured using UVA radiometer.

Exposure time was calculated in seconds using the formula:

$$\text{Time } (in\ sec) = \frac{\text{Required dose } (J/cm^2) \times 1000}{\text{Irradiance } (MW/cm^2)}$$

In our study all patients belonged to the skin phototype IV and V and hence treatment was started with 4 J/cm^2. Subsequent increments of 0.5J/cm^2 were given based on response to therapy and presence or absence of erythema.

FOLLOW UP:

Patients were followed up every week until cessation of treatment. Complete haemogram, LFT, Blood urea, Serum creatinine was done every 2 months. Adverse effects reported by the patient or noticed were recorded. Only the emollient liquid paraffin was allowed to be applied topically.

Efficacy of treatment:

Severity and extent of psoriasis was evaluated using the Psoriasis Area Severity Index (PASI). Severity of erythema (E), Desquamation (D) and Induration (I) was recorded on a 5 point scale as follows:

0 = Nil

1 = Mild

2 = Moderate

3 = Severe

4 = Very severe

The area of involvement was recorded on a 7 point scale as follows:

0 = Nil

1 = <10%

2 = 10-30%

3 = 31-50%

4 = 51-70%

5 = 71-90%

6 = 91-100%

PASI was calculated as follows:

$$PASI = 0.1(E_H+I_H+D_H)A_H + 0.2(E_U+I_U+D_U)A_U + 0.3(E_T+I_T+D_T)A_T + 0.4(E_L+I_L+D_L)A_L$$

A - Area

H - head

U - upper limb

T - trunk

L - lower limb

Group 2- 20 patients of vitiligo vulgaris:

PUVA was started and administered in the same manner as mentioned above and was given twice weekly on Wednesdays and Saturdays. The total dose of PUVA in each sitting did not exceed 8J/cm^2. The period of study was taken as 6 months and the degree of pigmentation was assessed every month based on Vitiligo Area Severity Index (**VASI**) score.

The percentage of vitiligo involvement is calculated in terms of hand units. One hand unit, which encompasses the palm plus the volar surface of all digits, is approximately equivalent to 1% of total

BSA. The degree of pigmentation is estimated to the nearest of one of the following percentages:

100% - complete depigmentation, no pigment present.

90% - specks of pigment present.

75% - depigmented area exceed the pigmented area.

50% - pigmented and depigmented areas equal.

25% - pigmented area exceeds depigmented area.

10% - only specks of depigmentation present.

The VASI for each body region is determined by the product of the area of vitiligo in hand units and extent of depigmentation within each hand unit measured patch.

Total body VASI = All body sites (Hand units) × (residual depigmentation).

Group 3 - 10 patients with generalized lichen planus were included for PUVA therapy. The PUVA was started as mentioned above and given for a period of approximately 3 months. The activity of the disease was noted by selecting a particular area like one hand or one leg and the number of papules in that area was counted approximately. The number of papules was counted again in the same area every month. Symptomatic improvement as told by the patient as well as the side effects was noted.

Group 4 - 5 patients of parapsoriasis. PUVA was started as mentioned above and continued for an average of 3 months. The percentage of involvement calculated initially by hand unit method which is equal to 1% and the improvement calculated every month. The side effects were also noted.

OBSERVATION AND RESULTS

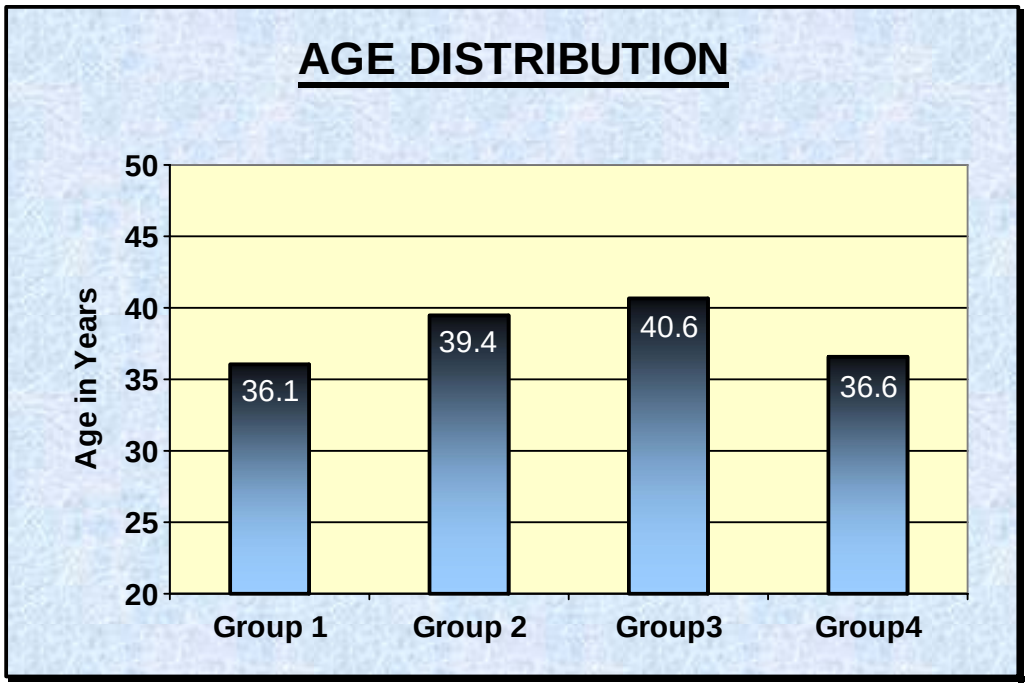
AGE DISTRIBUTION-

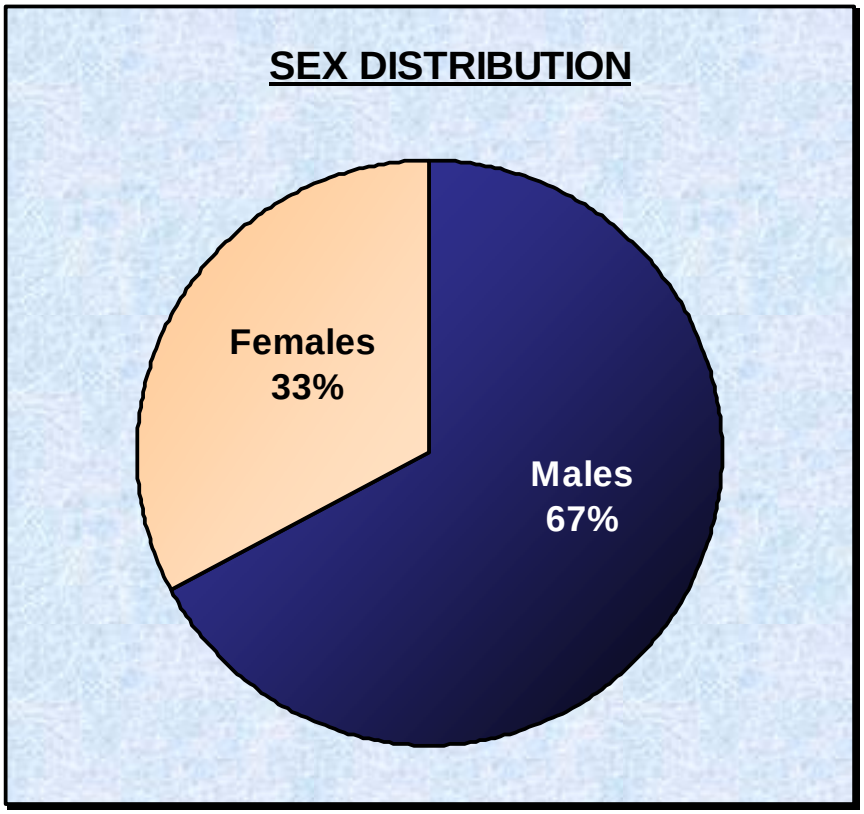
The mean age in various study groups were as follows:

GROUP	Mean Age *(years)*	Range (*years)*
1	36.1	23 – 60
2	39.4	20 - 54
3	40.6	30 - 56
4	36.6	32 – 40

SEX DISTRIBUTION-

GROUP	MALES	FEMALES
1	15	5
2	12	8
3	6	4
4	4	1


AGE DISTRIBUTION
Age in Years
50
45
40
35
30
25
20
36.1
39.4
40.6
36.6
Group 1
Group 2
Group3
Group4


SEX DISTRIBUTION
Females
33%
Males
67%

DURATION OF ILLNESS-

Group	Mean Duration of illness
1	2.15 yrs
2	5.2 yrs
3	1.15 yrs
4	5.4 months

FAMILY HISTORY-

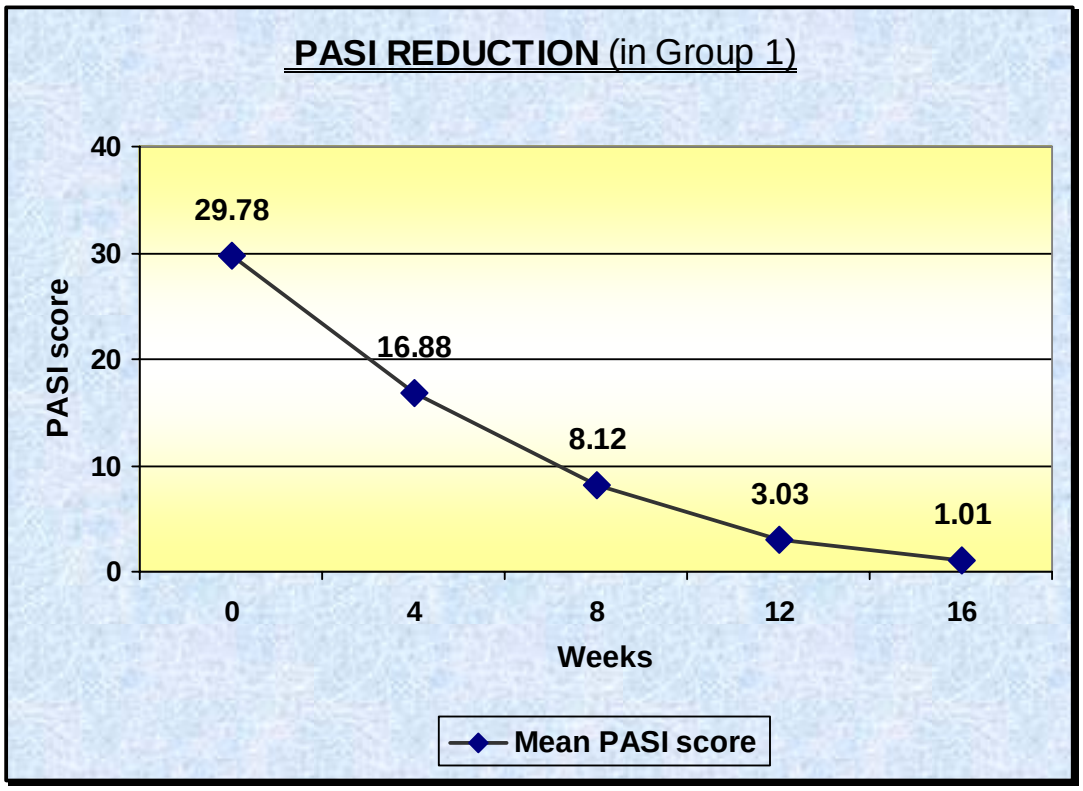
Family history was elicited in group 1 and 2.

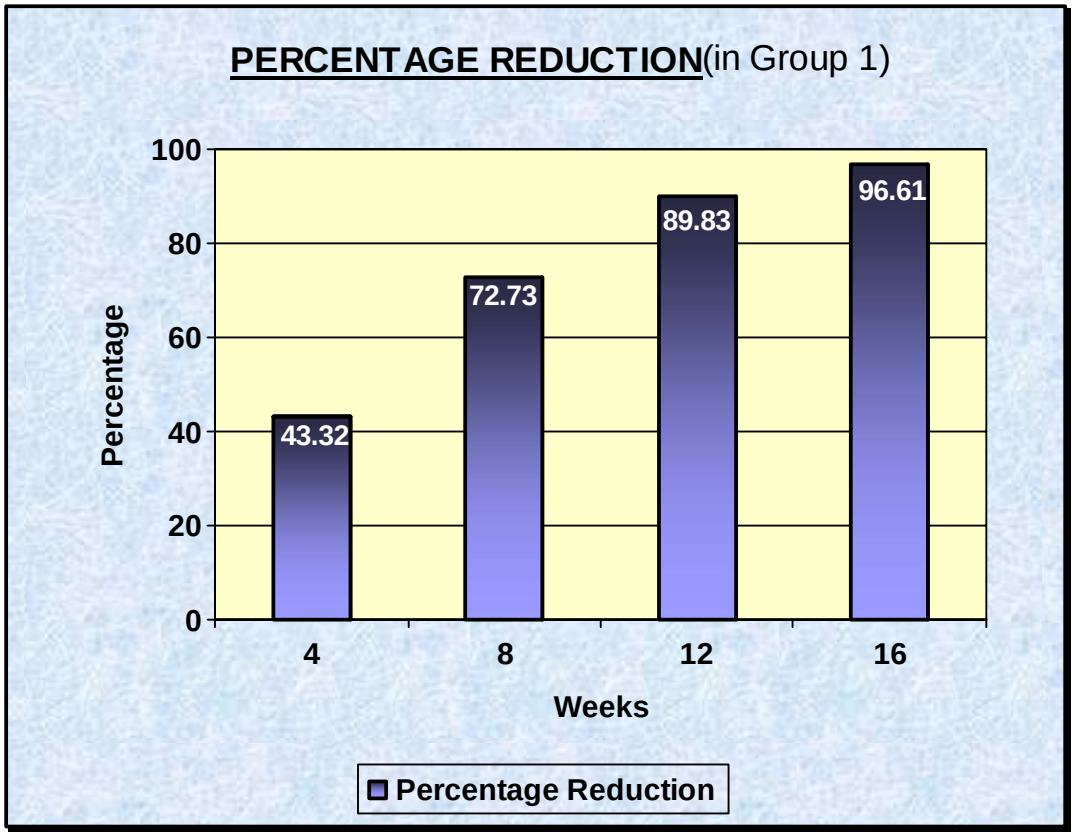
Group	% of family history
1	10
2	0

Group 1: **REDUCTION IN PASI SCORE** :

The mean PASI scores at 0, 4, 8, 12 and 16 weeks have been tabulated and the reduction depicted in Figure below.

The graph in the figure shows the gradual reduction in PASI, with a mean PASI score of 29.78 at 4 weeks, 16.88 at 8 weeks, 8.12 at 12 weeks, 1.01 at the end of 16 weeks. These values correspond to a percentage reduction of 43%, 72%, 89% and 96% at the end of 4, 8, 12, and 16 weeks respectively as depicted in Figure below.


PASI REDUCTION (in Group 1)
40
30
20
10
0
PASI score
29.78
16.88
8.12
3.03
1.01
0
4
8
12
16
Weeks
Mean PASI score


PERCENTAGE REDUCTION (in Group 1)
100
80
60
40
20
0
Percentage
43.32
72.73
89.83
96.61
4
8
12
16
Weeks
Percentage Reduction

MEAN CUMULATIVE UVA DOSE AND NUMBER OF UV EXPOSURES AND TOTAL DURATION OF TREATMENT

	Group 1
Average no. of UVA exposures	32 (26-40)
Duration of treatment(weeks)	16.14 (13-20)
Mean cumulative UVA dose	244 (216-265)

RESPONSE TO THERAPY

Based on the percentage reduction in PASI results were graded as excellent, good and moderate.

Results	***No. of patients***	***Percentage***	***% reduction in PASI score at 16 weeks***
Excellent	14	70%	>95%
Good	4	20%	80-95%
Moderate	0	0%	50-80%

In this group one patient had exacerbation of lesions and one patient discontinued therapy.

STATISTICAL ANALYSIS:

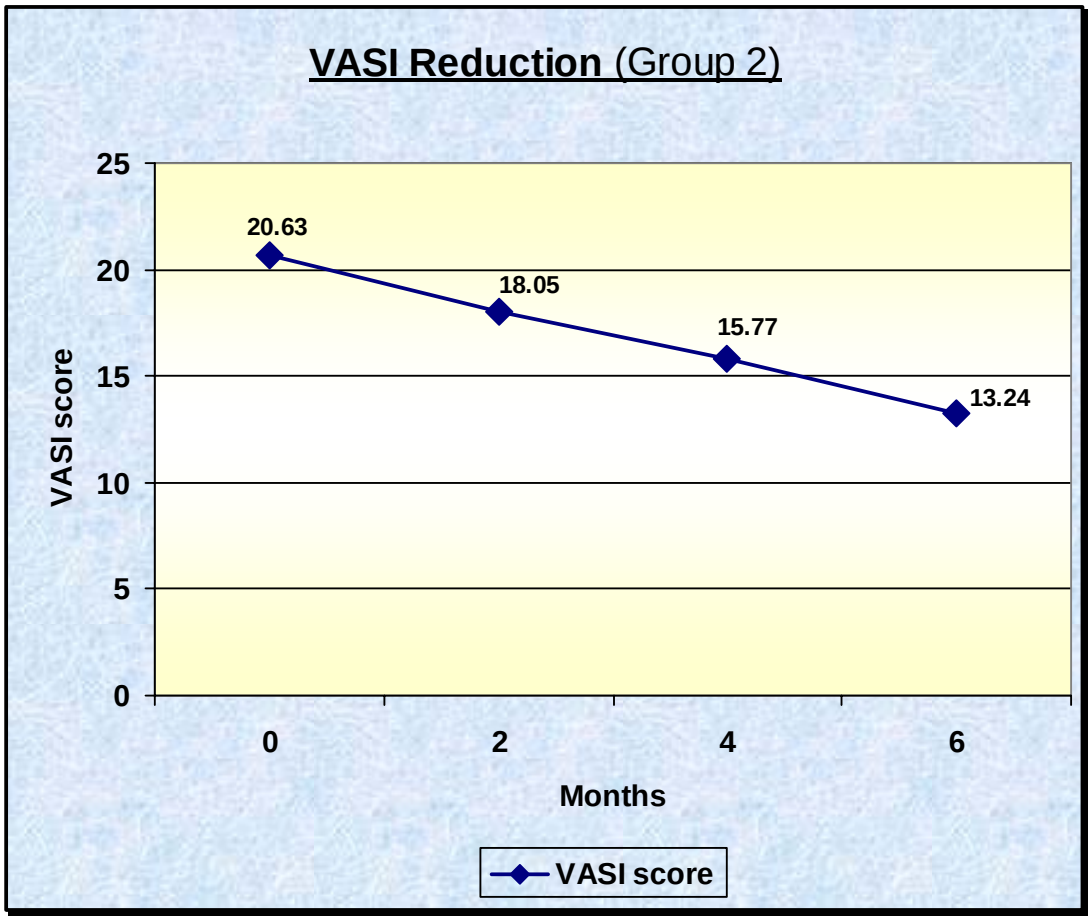
While performing a Regression Analysis with the input factors being the initial PASI score (PASI 0) and cumulative UVA dosage across 16 weeks we are able to arrive at the regression equation for the final

PASI score at the end of 16th week (PASI 16). The P value obtained from the test is 0.015.

Any P value <0.05 is considered statistically significant. Hence our P value of 0.015 implies that there is a significant reduction in PASI score after PUVA therapy.

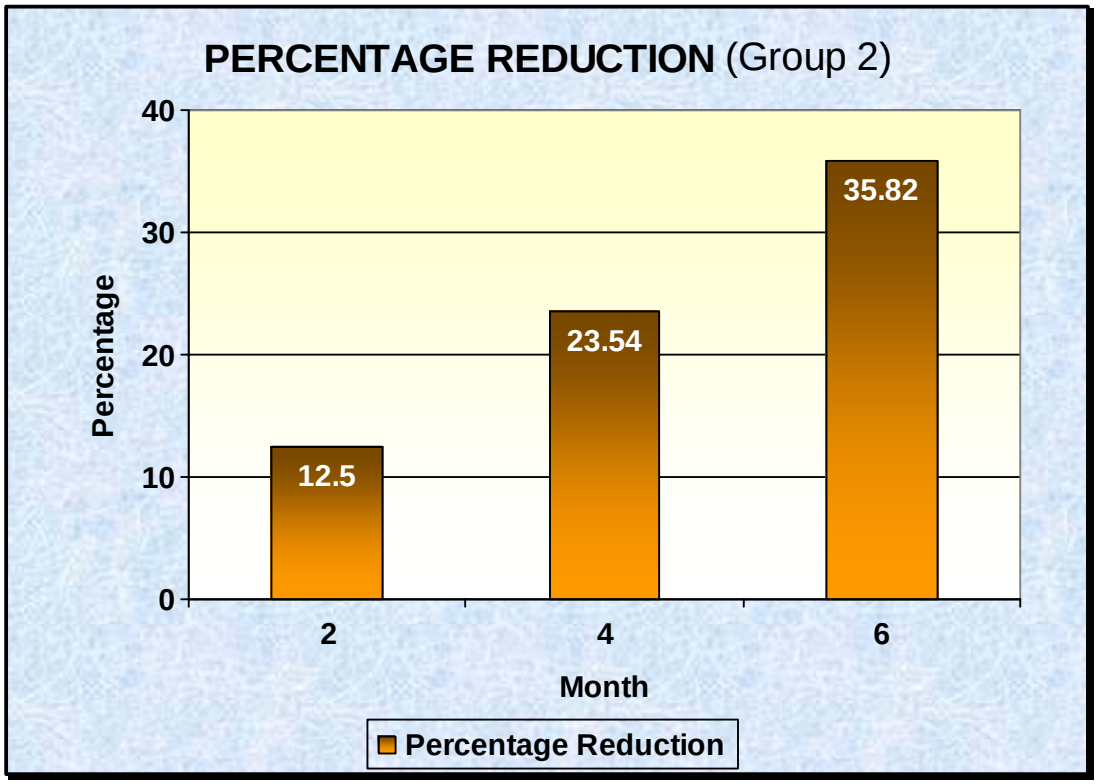
Group 2 : REDUCTION IN VASI SCORE:

The mean VASI score at 0, 2, 4, 6 months has been tabulated and its reduction depicted in Figure below



PERCENTAGE REDUCTION IN VASI:

The percentage reduction in VASI score were 12.5%, 23.4%, 35.82% in 2, 4 and 6 months respectively as depicted in figure below:



MEAN CUMULATIVE DOSE AND NO.OF UV EXPOSURES:

	Group 2
Average no of UV exposures	60
Duration of treatment(months)	6 months
Mean cumulative UVA dose	273.05 J

RESPONSE TO THERAPY-Assessment of improvement in 6 months

Results	***No. of patients***	***Percentage***	***% of improvement in VASI score***
Poor response	2	10%	1-25%
Moderate response	17	85%	25-50%
Good response	0	0	51-75%
Excellent response	0	0	>76%

One patient discontinued treatment on her own.

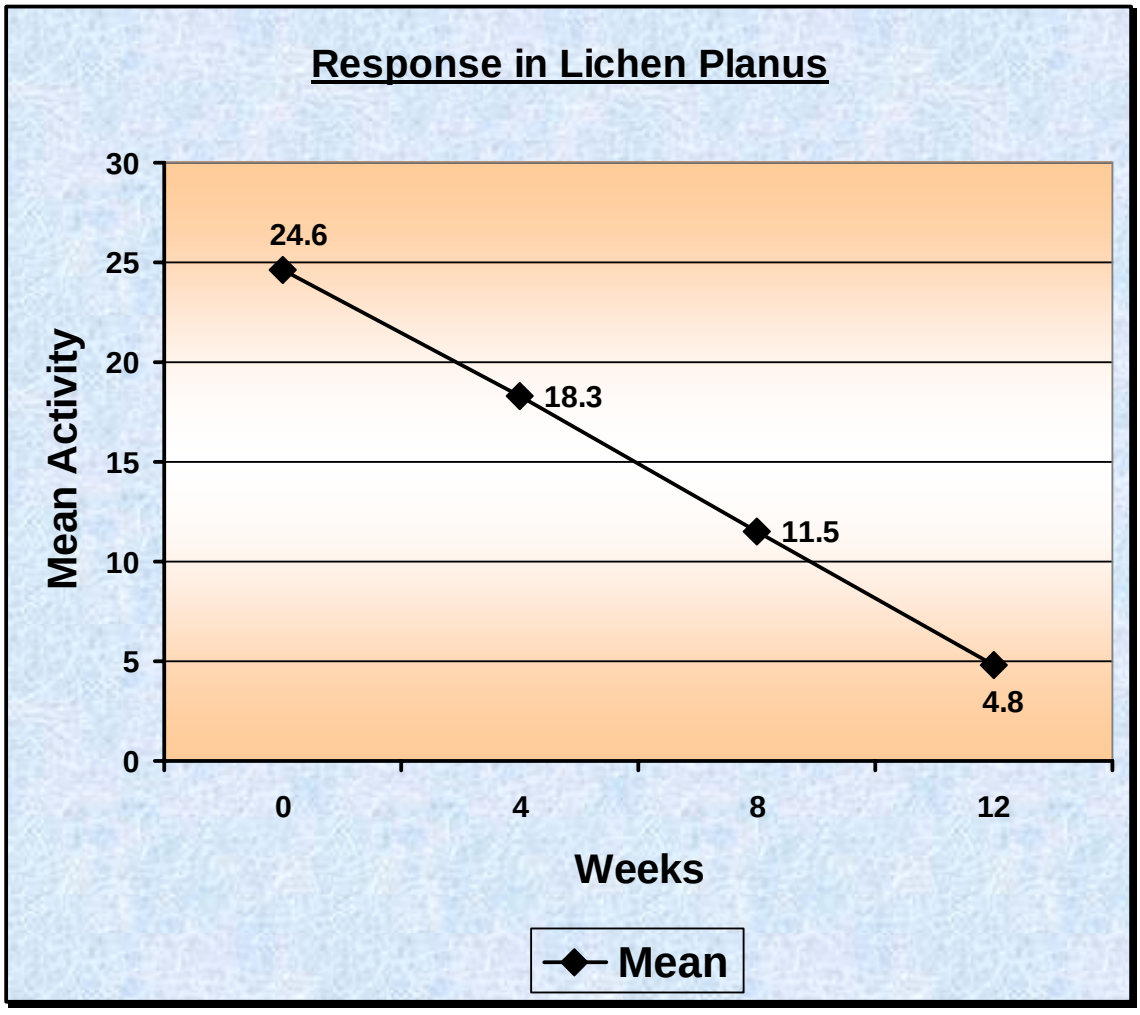
STATISTICAL ANALYSIS:

While performing a Regression Analysis with the input factors being the initial VASI score (VASI 0) and cumulative UVA dosage across 6 months we are able to arrive at the regression equation for the final VASI score at the end of 6^{th} month (VASI 6). The P value obtained from the test is 0.012.

Any P value <0.05 is considered statistically significant. Hence our P value of 0.012 implies that there is a significant reduction in VASI score after PUVA therapy.

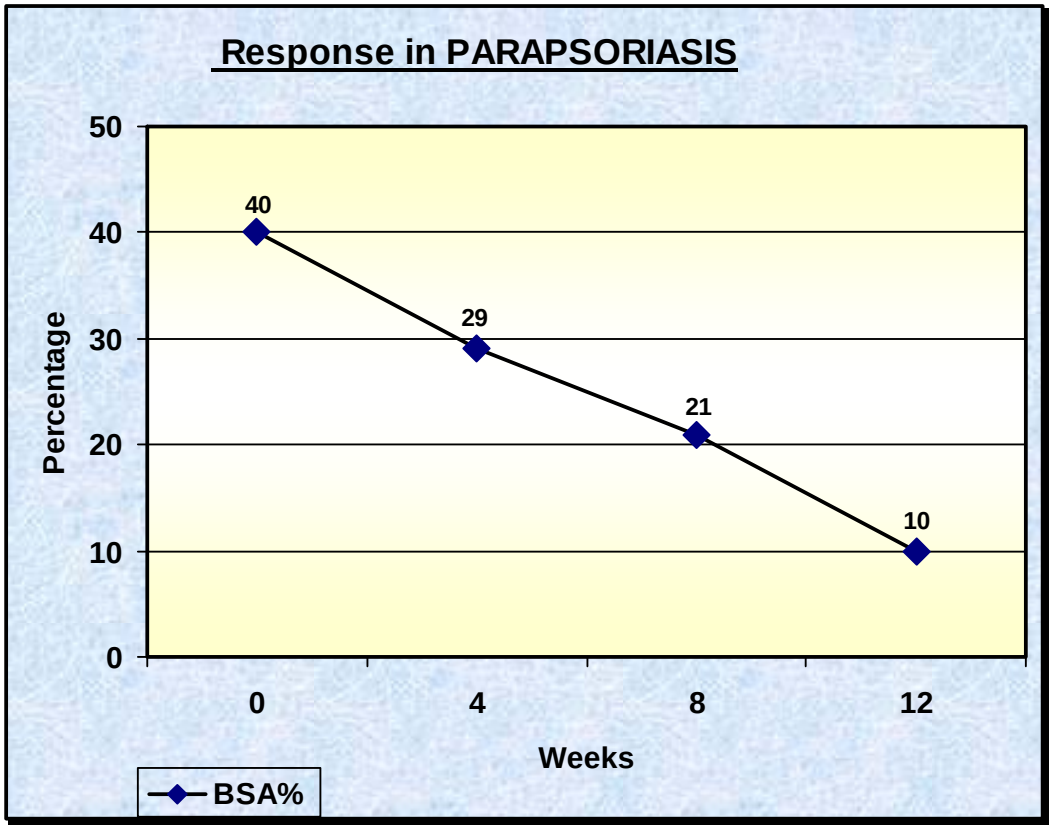
Group 3 – Lichen planus:

The improvement of lichen planus lesions was assessed based on decrease in the number of papules in a targeted area .The mean number of papules at 0, 4, 8 and 12 weeks is depicted in the figure below.



Group 4

The assessment of improvement of parapsoriatic lesions were made on the reduction in body surface area involved. The mean BSA at 0, 4, 8 and 12 weeks is shown in figure below.



Two patients responded poorly to the therapy.

ADVERSE EFFECTS:

The common adverse effects seen in all patients undergoing PUVA has been tabulated:

Side effects	***Group 1***	***Group 2***	***Group 3***	***Group 4***
Nausea	3	1	0	1
Pruritus	2	2	2	0
Erythema	2	3	1	0

A total of 5 patients had nausea after taking psoralen tablet. 6 patients had pruritus which was exaggerated during the first few weeks of therapy. 6 patients also had erythema after treatment.

DISCUSSION

Group 1

The efficacy of PUVA in the treatment of psoriasis has been documented and confirmed by various clinical trials in many parts of the world.

In our study the number of patients who had excellent response were 14 (70%) and a good response were 4 (20%). 50% reduction in PASI was seen by 8 weeks and the mean duration of treatment was 16.4 weeks and a the mean cumulative dose of 244 Joules. Hence our study results show that PUVA is a good therapeutic option for the treatment of psoriasis.

In the U.S. Cooperative Clinical Trial (USCCT), percentage of patients with marked improvement of complete clearing were 88% whereas in our study it was 70%. Cumulative UVA dose in the USCCT was 245 Joules.[68]

Though our study was of a low number, the results were consistent with those of the U.S. multicenter trial and other international studies

Group 2

In our study about 17 patients (85%) showed a moderate response within 6 months of treatment. The response was noted only after 6-8 weeks after therapy initially.

However we also noted that sites like the trunk, arms and legs responded well whereas the acral regions, periorificial regions and bony prominences did not respond well to treatment. The response is better if PUVA is continued for 9-12 months as various studies indicate. To avoid the long term complications our patients were given PUVA for only 6 months and the efficacy noted. The patients were then advised to continue on PUVASOL and this improved pigmentation. The perifollicular type of repigmentation was the commonest type noted.

Our study is comparable with that done in St. John's Institute of Dermatology, London, which shows that PUVA is moderately effective in widespread vitiligo.[74] Though our study showed only moderate effect in Vitiligo vulgaris, it still continues to be a good option as the patients had been affected for a long duration.

Group 3

The improvement noted in generalized lichen planus was also satisfactory. 80% of the patients showed good symptomatic response within 2-4 weeks of therapy. There was flattening of the papular lesions and disease activity was controlled well. However patients had postinflammatory hyperpigmentation.

Our study is comparable to the study done by Gonzalea E, et al.[78]

Group 4

Parapsoriasis is considered to be one of the indications of PUVA therapy. As mentioned in the study done by Westphal H, Walter A, et al.,[75] three patients in our study showed 90% clearance of lesions within 3 months of therapy. However two patients did not respond satisfactorily. But still PUVA should be considered a therapeutic option for parapsoriasis.

The adverse effects noted in our study were all minor, none of which required cessation of treatment. Nausea was a side effect seen in about 6 patients which improved once the patients were advised to take the drug after having a light meal. A few patients had increased pruritus during the initial few weeks of treatment which improved after sometime and supportive measures like antihistamines.

Erythema was another side effect noted. But it was mild in most of the cases which improved with topical calamine application.

However the patient compliance was not satisfactory as patients had to come twice weekly to the hospital for treatment. Short therapy had better compliance than long term therapy like vitiligo therapy. A good motivation and counseling were useful to improve compliance.

CONCLUSION

1. PUVA is an effective and safe therapy for the treatment of Psoriasis vulgaris as evidenced by the response rate of 90% seen in our study with only minimal side effects like erythema, nausea and pruritus.
2. PUVA also induces a moderate amount of repigmentation in Vitiligo vulgaris during 6 months of therapy. Hence careful patient counselling is needed before starting PUVA, as it takes a long duration to induce extensive repigmentation.
3. PUVA also results in satisfactory improvement in generalized Lichen planus and helps in the clearance of Parapsoriasis.
4. Thus PUVA can be considered a valuable mode of therapy for the above conditions like Psoriasis vulgaris, generalized Lichen planus and Parapsoriasis. It is also useful in Vitiligo when patient does not respond to other modalities of treatment.

Group 1: **PSORIASIS VULGARIS** – Before and After 16 weeks of treatment.

Group 1: **PSORIASIS VULGARIS** – Before and After 16 weeks of treatment.

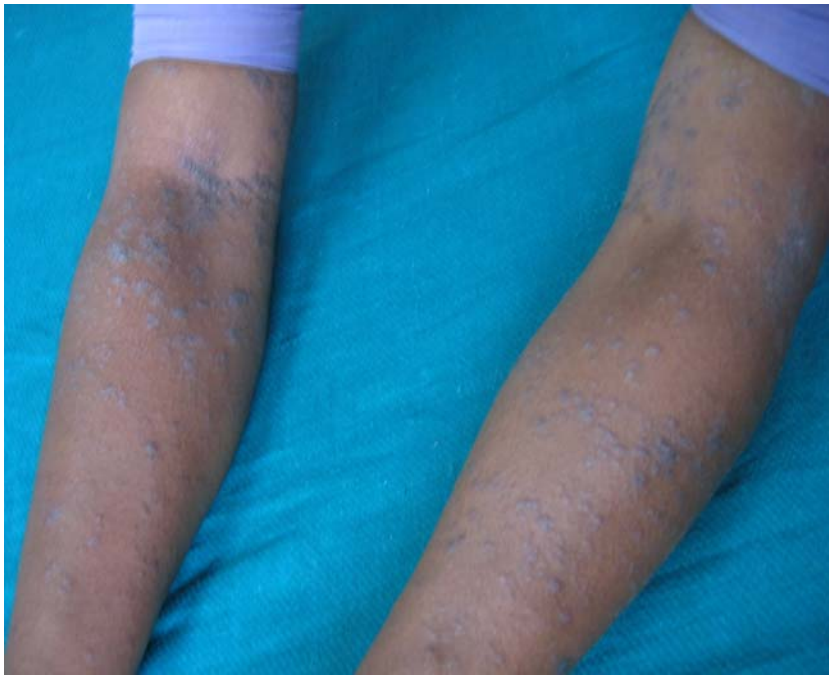
Group 1: **PSORIASIS VULGARIS** – Before and After 16 weeks of treatment.

Group 2: **VITILIGO VULGARIS** – Before and after 6 months treatment

Group 2: **VITILIGO VULGARIS** – Before and after 6 months treatment

Group 2: **VITILIGO VULGARIS** – Before and after 6 months treatment

Group 3: **LICHEN PLANUS** – Before and After 12 weeks of treatment.



Group 3: **LICHEN PLANUS** – Before and After 12 weeks of treatment.

Group 4: **PARAPSORIASIS** – Before and After 3 months of treatment.

Group 4: **PARAPSORIASIS** – Before and After 3 months of treatment.

Erythema after PUVA therapy

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PROFORMA

Name: Date:

Age/Sex: OP No:

Occupation:

Address: Case No:

HISTORY

Duration: years months

Itching: ☐ Yes ☐ No

H/o Previous Treatment: Topical Systemic

EXACERBATION WITH:

☐ Cold climate ☐ Sunlight ☐ Dialysis

☐ Infection ☐ Trauma ☐ Emotional Factors

☐ Puberty ☐ Pregnancy ☐ Menopause

Past History:

☐ Hypertension ☐ Diabetes ☐ TB ☐ IHD

☐ Thyroid disorders ☐ Asthma ☐ Photosensitivity

☐ Cutaneous malignancy ☐ Radiotherapy

☐ Pregnant ☐ Lactating mother

Drugs taken for any other condition:

Family History: ☐ Mother ☐ Father

☐ Sibling ☐ Others

Personal History: ☐Alcohol ☐Smoking

Menstrual History:

GENERAL EXAMINATION:

☐ Pallor ☐ Icterus ☐ Edema

Pulse: BP:

Weight:

SYSTEMIC EXAMINATION:

CVS:

RS :

P/A :

CNS :

Musculoskeletal:

ENT :

Dental:

DERMATOLOGICAL EXAMINATION

Skin lesions: Site

Morphology

Surface area involved

Signs

Mucous membrane

Palms and soles

Scalp

Hair

Nail

DIAGNOSIS:

INVESTIGATIONS:

Blood Sugar: Urea: Creatinine:

Blood VDRL HIV: Skin biopsy:

Ophthalmological examination:

Date					
Hb					
TC					
DC					
ESR					
Platelets					
SGOT					
SGPT					
SAP					
Total Protein					
Total Bilirubin					

PUVA CHART:

Date	***Cycle***	***Dose***	***Duration***	***Cumulative Dose***	***Side Effects***

FOLLOW UP:

In Psoriasis Vulgaris:

Week	PASI Score	Cumulative dose
0		
4		
8		
12		
16		

In Vitiligo vulgaris:

Months	VASI Score	Cumulative dose
0		
2		
4		
6		

In Lichen planus: ***Area chosen:***

Week	No. of papules	Cumulative dose
0		
4		
8		
12		

In Parapsoriasis:

Week	BSA%	Cumulative dose
0		
4		
8		
12		